長年患者団体が中心となり，国の助成を要望してきたが，2009年10月に特定疾患治療研究事業の対象疾患に認定され，支払った医療費に対し公費による払い戻しが受けられるようになった．しかし，有効な治療があってこそ，こうした国の助成が生かされるというものである．

一方，前世紀の終わりにLAMの病因が解明された．細胞のがん抑制遺伝子TSC－1またはTSC－2に点変異が生じることにより，下流にあるmTORの抑制が効かなくなり，その細胞が異常増殖するために発症することが明らかにされた．mTOR阻害薬のシロリムスが治療薬の候補に挙がり，シンシナティの腎臓病グループが中心となり，2003～04年に第Ⅰ・Ⅱ相試験（CAST試験）が行われた．後腹膜血管筋脂肪腫の大きさの減少を主要評価項目として，患者25例にシロリムスを1年間投与した結果，血管筋脂肪腫の大きさがMRI上で平均53.2％縮小した．驚きだったのは，期待していなかった肺一秒量や努力性肺活量の改善が見られたことである[2]．そこで，同大学のフランクマッコーマック教授らが呼びかけ，肺稀少疾患コンソーシアムのメンバーが動いて，シロリムスのLAMへの有効性と安全性を検証するためのMILES試験が計画された．

国際共同臨床試験の困難な道のり

稀少疾患でも何カ国もが協力すれば，困難な二重盲検試験が可能になるー言うは易く行うは難しで，我々には様々な困難が立ちはだかっていた．日本で稀少疾患に対する新薬の実用化を目指すには，医師主導の治験と未承認薬・適応外検討会議を通す方法があるが，どちらも数年以上を要し，治験には莫大な費用もかかる．また，治験届を申請すると医薬品医療機器総合機構からプロトコールの変更を求められるのは目に見えていた．日本と米国・カナダでは医療制度があまりに異なるからである．マッコーマック教授と協議し，日本では2施設の自主臨床研究としてMILES試験に参加し，米国では日本の臨床試験の主任研究者をマッコーマック教授が務める医師主導の治験として米食品医薬品局（FDA）に提出するという変則的な形を取ることとした．同試験で有効性と安全性を証明し，その後日本で薬事承認を目指すこととなった．

2006年にスタートしてから，患者登録まで，準備期間には約2年間を要した．プロトコルを和訳し，それをさらにバックトランスレートして米国試験本部に送り審査してもらい，米国の倫理委員会での再承認，試験スタッフの倫理教育，プロトコルトレーニングなどの過程と患者向けのMILES試験説明会を行った．2007年11月に米国試験本部からプロジェクトマネージャーが来日し，近畿と新潟の施設を監査し，スタッフに教育をした．その後，試験本部と研究費の契約交渉が開始され，2008年2月に成立した．薬剤の無償供与をしてくれるワイス社との交渉，成立を経て，2008年4月，近畿中央胸部疾患センターと新潟大学医歯学総合病院がサイトオープンした．

研究費も決して潤沢ではなかった．2007年4月－2010年3月までは，幸い厚生労働科学研究費補助金の臨床試験推進事業で外部業者とも委託契約ができたが，期限終了後は，米国の患者支援団体―LAM財団に泣きついてなんとか試験終了にこぎ着けた．LAM財団は，試験中，日本人のLAM患者が新潟と近畿に来院するときの交通費も負担してくれていた．

試験の概要

MILES試験では，18歳以上の女性のLAM患者で，中等～重症患者を対象とした．2006年12月～10年9月に111例が登録され，89例が適格とされた．シロリムスを1日2mg投与する群（46例）とプラセボを投与する群（43例）にランダムに割り付け，投与期間と観察期間に各1年間を予定した．主要評価項目は肺一秒量の1ヵ月間の変化量，副次的評価項目は，努力性肺活量の改善や肺気量，精密肺機能検査，6分間歩行距離，VEGF－D値，QOLのスコアなどの1年間の変化とした．

全例が1年間の服薬を終了する2010年9月初

旬まで試験は続行されたが，予算不足から観察期間は打ち切られ，最終解析が2010年11月に行われた．

シロリムスの効果に改めて驚く

MILES試験中から新潟に来院される患者さんの様子から，シロリムスが効いているのではないかと期待を持っていたが，一昨年の暮れにフランクマッコーマック教授からその結果を聞いたときは震えた．投与期間中の1ヵ月間のFEV1.0の変化量は，プラセボ群の−12±2mLに対し，シロリムス群は1±2mLで有意差が認められた（P＜0.001，**図2**）．投与期間1年間のFEV1.0の変化量は，プラセボ群に対しシロリムス群で153mL少なかった．投与期間のFVCの変化量は，プラセボ群の−129±233mLに対し，シロリムス群は97±260mLとなった（P＝0.001，**図2**）．ただし，肺機能が改善したのはシロリムス群の約半数にとどまった．さらに，VEGF-D値，包括的な健康関連のQOLのスコアなども，投与期間にシロリムス群で有意に改善した．控えめに評価しても，シロリムスはLAM患者の一部で肺機能の低下を遅らせる効果があるといえる．またVEGF-D値については，治療効果のバイオマーカーとなる可能性がある．

試験のもう一つの目的はシロリムスの安全性の確認だったが，皮疹，口内炎，下痢，脂質異常症などの有害事象は，プラセボ群と比べてシロリムス群で頻度が高かったが，多くは軽症であった．入院を要する重症の有害事象の頻度は，両群で有意差はなかった．ただし，海外でシロリムス群の患者1例に心膜炎が発生し，心タンポナーデに進行した（ICUで治療後回復した）．

薬事承認までのシナリオ

3月にMILES試験の結果が報道され，患者の中には，シロリムスを個人輸入する人も現れている．危惧されるのは，医師に伝えないことである．LAMではシロリムスの長期服用が必要と考えられるが，長期的な安全性のデータはなく，今後の課題である．また，MILES試験では除外された患者でも，効く可能性もある．試験とは別にシロリムスを用いたところ，劇的に改善したケースがあった．この患者は乳糜胸水の貯留で試験に参加できなかった．呼吸困難がHugh-Jones分類のV度となり，入院と胸水ドレナージ，HOTを要した．患者の強い希望でシロリムスの服用を続行すると，投与開始後約3ヵ月で胸水が徐々に減少し，呼吸困難が軽減．約8ヵ月でHOTから完全に離脱，約1年で社会復帰した．

製造販売元は，ワイス社からファイザー社へと移ったが，2011年6月，ファイザー社は日本での

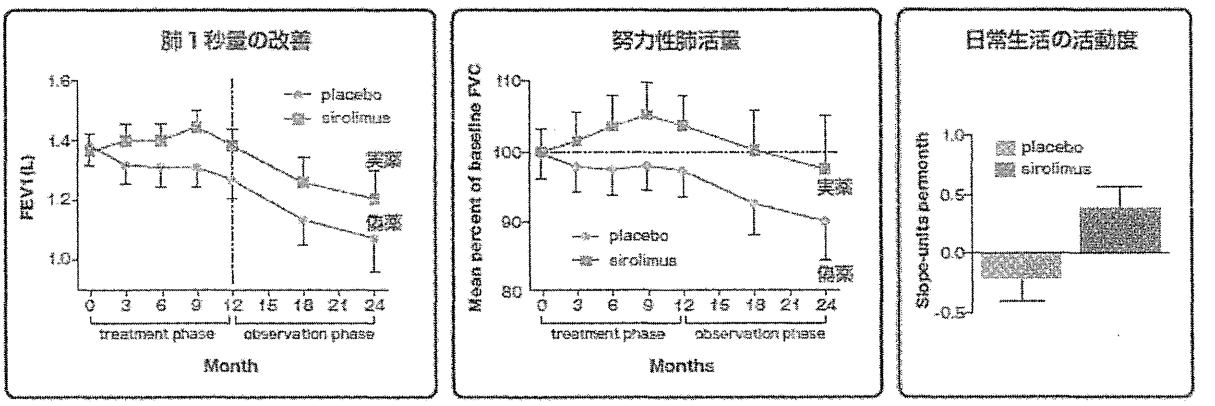

図2　MILES試験の有効性：左：肺1秒量の経時的変化　中：努力性肺活量の経時的変化
右：日常生活の活動量（QOL）の一年間の改善度　■実薬　□偽薬

薬事承認申請はしないことを決めた．その代わり，日本ではシロリムスを他社へライセンスアウトする方針を決め，ノーベルファーマ社が販売権を得た．一方，日本で多くのLAM患者が安全にシロリムスを服用できるようにするため，生命科学医療センターと第二内科呼吸器グループは医師主導治験を企画した．この企画は，2012年4月厚生労働科学研究費難治性疾患等克服研究事業に採択された．6月29日医薬品医療機器総合機構に治験届を提出し，9月5日より全国9施設共同医師主導治験が開始された．順調に進めば2013年6月に薬事承認申請を行ない，2014年3月に承認の見込みである．

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Computed tomographic features of lymphangioleiomyomatosis: Evaluation in 138 patients

Kazunori Tobino[a,b,c,*], Takeshi Johkoh[d], Kiminori Fujimoto[e], Fumikazu Sakai[f], Hiroaki Arakawa[g], Masatoshi Kurihara[c,h], Toshio Kumasaka[c,i], Kengo Koike[b], Kazuhisa Takahashi[b], Kuniaki Seyama[b,c]

[a] Department of Respiratory Medicine, Iizuka Hospital, 3-83 Yoshiomachi, Iizuka, Fukuoka 820-0018, Japan
[b] Division of Respiratory Medicine, Juntendo University Faculty of Medicine & Graduate School of Medicine, 2-1-1 Hongo, Bunkyo-Ku, Tokyo 113-8421, Japan
[c] The Study Group of Pneumothorax and Cystic Lung Diseases, 4-8-1 Seta, Setagaya-Ku, Tokyo 158-0095, Japan
[d] Department of Radiology, Kinki Central Hospital of Mutual Aid Association of Public School Teachers, Kurumazuka 3-1, Itami, Hyogo 664-0872, Japan
[e] Department of Radiology, Kurume University School of Medicine and Center for Diagnostic Imaging, Kurume University Hospital, 67 Asahi-machi, Kurume, Fukuoka 830-0011, Japan
[f] Department of Diagnostic Radiology, Saitama International Medical Center, Saitama Medical University, 1397-1 Yamane, Hidaka, Saitama 350-1298, Japan
[g] Department of Radiology, Dokkyo Medical University, 880 Kita-Kobayashi, Mibu, Tochigi 321-0293, Japan
[h] Pneumothorax Center, Nissan Tamagawa Hospital, 4-8-1 Seta, Setagaya-Ku, Tokyo 158-0095, Japan
[i] Department of Pathology, Japanese Red Cross Medical Center, 4-1-22 Hiroo, Shibuya-Ku, Tokyo 150-0012, Japan

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ABSTRACT

Purpose: The aim was to characterize the computed tomographic (CT) findings from Japanese patients with lymphangioleiomyomatosis (LAM).
Materials and methods: CT scans of the chest, abdomen, and pelvis from 124 patients with sporadic LAM (S-LAM, mean age, 37.4 years) and 14 patients with tuberous sclerosis complex (TSC)-LAM (mean age, 35.6 years) were analyzed.
Results: Pulmonary nodules (18.8%) and hepatic angiomyolipoma (AML, 24.3%) were more common in our patients than those in previous reports. Compared with TSC-LAM, S-LAM group had a higher frequency of pulmonary nodules (28.6% vs 32.3%, $P<0.01$) and lower frequencies of air-space consolidation (21.4% vs 2.4%, $P<0.01$), pneumothorax (28.6% vs 8.1%, $P=0.02$), pulmonary hilar lymphadenopathy (14.3% vs 0.8%, $P<0.01$), renal AML (85.7% vs 17.4%, $P<0.01$), hepatic AML (71.4% vs 17.4%, $P<0.01$), and retrocrural lymphadenopathy (14.3% vs 1.4%, $P=0.04$). Axial lymphatic abnormalities (i.e., thoracic duct dilatation, lymphadenopathy, and lymphangioleiomyoma) were most common in the pelvis and tended to decrease in incidence with increased distance from the pelvis.
Conclusion: The incidence of some CT findings in Japanese patients differed from those in previous reports. Axial lymphatic abnormalities noted here suggest that the origin of LAM cells may be the pelvis.

1. Introduction

Lymphangioleiomyomatosis (LAM) is an uncommon disease in females of child-bearing age and is characterized by the proliferation of abnormal smooth muscle cells (LAM cells) in the lungs and along the axial lymphatic system of the thorax, retroperitoneum, and pelvic cavity. LAM occurs in approximately 30% of females with tuberous sclerosis complex (TSC-LAM), although LAM also occurs in females without TSC (i.e., sporadic LAM [S-LAM]) [1]. Both TSC-LAM and S-LAM are associated with mutations in the *TSC* genes. A diagnosis of LAM is usually made when warranted by clinical history and a pathognomonic appearance of pulmonary cysts on chest computed tomography (CT) or identification in a pathology report of LAM cells [2,3]. Recently, clinical and radiographic characteristics of patients with LAM were described based on the analyses of a large series of patients in National Heart, Lung, and Blood Institute (NHLBI) LAM registry [4–6]. In our country, clinicopathologic findings of 46 patients with LAM were already reported [2]; however,

* Corresponding author at: Division of Respiratory Medicine, Juntendo University Faculty of Medicine & Graduate School of Medicine, 2-1-1 Hongo, Bunkyo-Ku, Tokyo 113-8421, Japan. Tel.: +81 3 5802 1063; fax: +81 3 5802 1617.
E-mail address: tobino@juntendo.ac.jp (K. Tobino).

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no comparable radiologic investigations have been done. Therefore, we retrospectively examined the CT images from a large series of Japanese patients with LAM to clarify the spectrum and prevalence of radiologic findings in our country.

2. Materials and methods

2.1. Patients

This retrospective study was approved by the ethics committee of our institution (JIRB21-134). We evaluated 138 females, including 124 patients with S-LAM (age range, 21–61 years; mean, 37.4 years) and 14 patients with TSC-LAM (age range, 25–50 years; mean, 35.6 years) who had undergone at least one of the following examinations at our hospital between May 1990 and November 2009: chest CT scans (138 patients; age range, 21–61 years; mean, 37.3 years), abdominal CT scans (72 patients; age range, 22–61 years; mean, 36.9 years), and pelvic CT scans (69 patients; age range, 22–61 years; mean, 37.0 years). All patients were studied when there was no evidence infection and large pneumothorax (the presence of a visible rim of ≥2 cm between the lung margin and the chest wall). Thirty-three of 138 patients had smoking history (mean, 7.6 pack-year). Each diagnosis was established based on biopsy findings of the lungs, lymphangioleiomyoma (LALM), lymph nodes (LNs), and uterus, respectively, in 92, 18, 3, and 1 patients. One patient was diagnosed based on a cytological study of the pleural fluid. Twenty-three patients did not undergo tissue biopsies, but had characteristic clinical pictures (recurrent pneumothorax and/or chylous pleural effusion) and CT findings (diffusely scattered thin-walled pulmonary cysts). Fourteen patients with TSC were diagnosed based on established clinical criteria [7].

2.2. CT technique

All chest CT scans were obtained at the end of inspiration by the patient in a supine position. The scanning protocol consisted of reconstruction of 1–5-mm collimation sections with a high spatial frequency algorithm at 1- or 2-cm intervals. Contrast material-enhanced abdominal and pelvic CT scans were performed in 62 and 60 patients, respectively, 100 ml of iohexol [Omnipaque 300] (Daiichi-Sankyo, Tokyo, Japan) or of iopamidol [Iopamiron 300] (Bayer Schering Pharma, Osaka, Japan). The remaining patients did not receive intravenous contrast material due to a history of either allergic reactions or poor renal function.

2.3. CT image analysis

Four radiologists, each with over 15 years of experience in chest, abdominal, and pelvic CT imaging, worked independently and had knowledge of the diagnosis (LAM only). These observers, all of whom were blinded to any other clinical information about the patients, were divided into two groups and reviewed the images in random order. Disagreements regarding the CT findings were resolved by consensus between the two groups. The CT scans were obtained on a variety of scanners. Images were evaluated on the film images or a monitor: (chest, 30 patients on film images and 108 patients on a monitor; abdomen, 27 patients on film images and 45 patients on a monitor; and pelvis, 25 patients on film images and 44 patients on a monitor) at window settings appropriate for viewing the lung (window level from −500 to −800 HU; window width from 1000 to 2000 HU), the mediastinum (window level from 15 to 40 HU; window width from 300 to 400 HU), and the abdomen and pelvis (window level from 15 to 40 HU; window width from 300 to 400 HU).

2.4. Chest CT image interpretation

Pulmonary cysts, noncalcified pulmonary nodules, ground-glass opacity, air-space consolidation, thickening of the bronchovascular bundles, interlobular septal thickening, thoracic duct dilatation, pneumothorax, pleural effusion, and lymphadenopathy (of the pulmonary hilum, mediastinum, supraclavicular, and/or axillary regions) were evaluated (see online supplementary materials for further details).

2.5. Abdominal and pelvic CT image interpretation

The abdominal and pelvic CT findings included hepatic and renal masses, LALM, lymphadenopathy (of the retrocrural space, upper abdomen, pelvis, and inguen), and ascites. Hepatic and renal masses were considered to represent angiomyolipomas (AMLs) if they contained fat. More information is provided in the online supplementary material.

2.6. Lymphatic lesions

Solitary masses found in LAM patients were considered to be possible LALMs or lesions of lymphadenopathy. Therefore, we defined "lymphatic lesions" as those involving thoracic duct dilatation, lymphadenopathy, LALM, and/or solitary masses and evaluated the frequency of such lesions in each part of the body.

2.7. Statistical analysis

The interobserver variation of the extent of pulmonary cysts was evaluated using Spearman's rank correlation coefficient. The interobserver variation of the extent and size of various abnormalities was evaluated using a linear regression analysis and Bland–Altman plots [8]. The interobserver variations among findings and the predominant distribution were analyzed using the k-statistic. Interobserver agreement was then classified as poor (0.00–0.20), fair (0.21–0.40), moderate (0.41–0.60), good (0.61–0.80), or excellent (0.81–1.00). The frequencies of various findings were compared using the Chi-square test with appropriate Fisher exact test, and the extent of pulmonary cysts was compared between the S-LAM and TSC-LAM groups using the unpaired t-test. All statistical analyses were performed using the SPSS software program (version 16.0, SPSS Inc., Chicago, IL, USA). The data are expressed as the mean ± standard deviation (SD). A P-value of less than 0.05 was considered to indicate a significant difference.

3. Results

3.1. Observer agreement

Regarding the chest CT findings, there was moderate to excellent agreement with respect to the extent and size of the pulmonary cysts (Spearman rank correlation coefficient, $r = 0.607–0.942$; $P < 0.001$) and fair to excellent agreement for the extent and size of abnormal lesions (linear correlation coefficient, $r = 0.352–0.942$; $P < 0.001$). Agreement was fair to excellent for the presence of abnormal findings and the characteristics of distribution ($k = 0.228–1.00$); an exception was the presence of pulmonary nodules ($k = 0.200$). Regarding abdominal and pelvic CT findings, the existence of abnormal findings generated good to excellent agreement ($k = 0.655–1.00$) and excellent agreement for the size of abnormal lesions (linear correlation coefficient, $r = 0.947–0.966$, $P < 0.001$), with the exception of the size of intrapelvic solitary masses ($r = 0.215$, $P = 0.580$) (see online supplementary materials for further details). Bland–Altman plots of the two groups' measurements of the extent of pulmonary cysts are shown in Fig. 1.

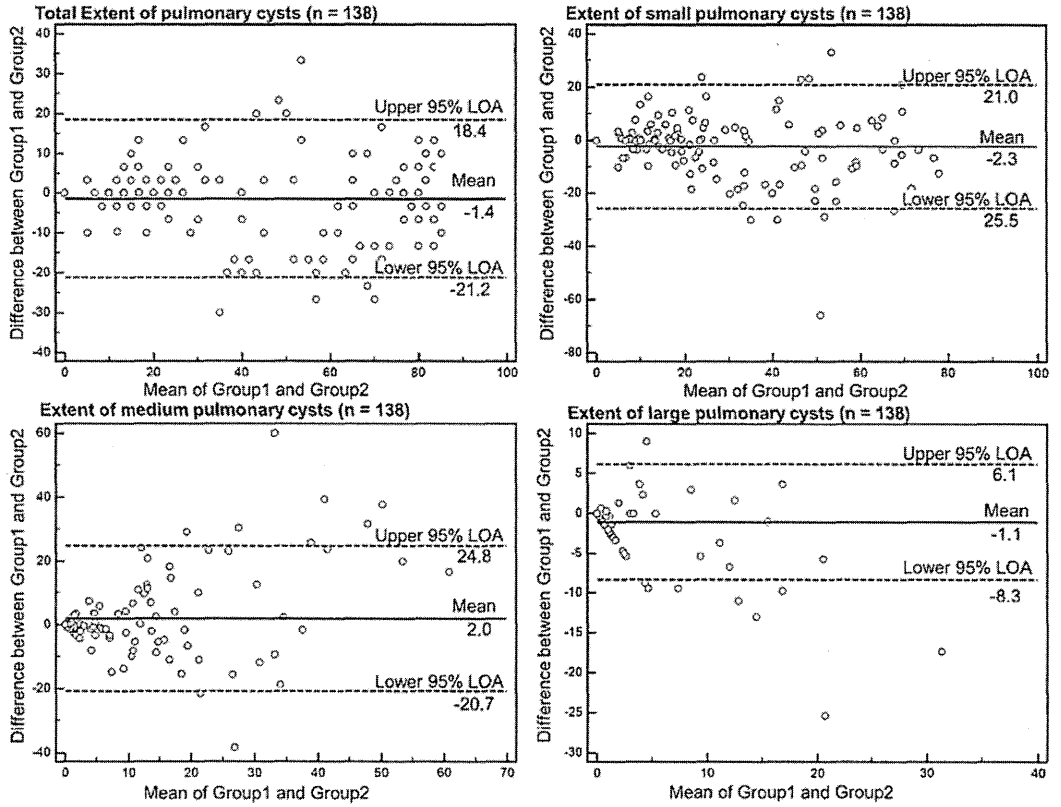

Fig. 1. Bland–Altman plots of measurements averaged across the two groups, according to lesion extent and size. Solid center line represents the mean of differences. The top dashed line shows the upper 95% limit of agreement (LOA), and the bottom dashed line shows the lower 95% LOA (±1.96 times the standard deviation).

The mean bias between the two groups was close to zero in each size category and also in total.

3.2. Chest CT findings

In our study, all but one patient had well-circumscribed, thin-walled pulmonary cysts. The total extent of pulmonary cysts on CT scans was 38.9 ± 27.9% (mean ± SD) (Table 1). Most pulmonary cysts were small (<10 mm) and distributed diffusely throughout the lungs. Most of our patients had randomly distributed pulmonary cysts.

The chest CT findings other than pulmonary cysts are also shown in Table 1. Fifty patients (36.2%) had noncalcified pulmonary nodules; of these, 26 (18.8%) had multiple (three or more) noncalcified pulmonary nodules. Ground-glass attenuation and air-space consolidation were found in seven (5.1%) and six (4.3%) patients, respectively. Thickening of the bronchovascular bundles and interlobular septal tissues were also relatively frequent (18.1% and 9.4%, respectively). Lymphadenopathy was more common in the mediastinum (8.7%) than in other regions of the thorax.

A diffusely thickened mediastinum with water attenuation was found in two patients (Fig. 2). Both patients also had pleural effusions and ground-glass attenuation.

3.3. Abdominal and pelvic CT findings

Of the 72 patients who underwent an abdominal CT, 17 (23.6%) had fat-containing masses, and three (4.2%) had uniformly enhanced masses in the kidneys (Table 2). These findings were thought to be indicative of AML; therefore, 20 (27.8%) patients may have had renal AML. Renal cysts were found in 5.6% of the present patients. Regarding the liver, 15 (20.1%) patients had fat-containing masses, and 3 (4.2%) patients had uniformly enhanced masses (Table 2). Therefore, the 18 (25.0%) patients considered to have liver AML. Liver cysts and hemangiomas were found in 13.9% and 1.4% of our patients, respectively. Lymphadenopathy was more common in the pelvis (11.6%) and abdomen (11.1%) than in other regions (Table 3). LALM afflicted 26 of 69 patients (37.7%) who underwent abdominopelvic CT, with LALM extending from the abdomen to the pelvis exhibiting the highest frequency (13.0%) (Table 3). Solitary masses were found in 14 of 69 patients (20.1%) who underwent abdominopelvic CT (Table 3). This finding was most frequently observed in the pelvis (11.8%). Nine of 72 patients (12.5%) had ascites ($k = 0.834$, $P < 0.001$).

3.4. Lymphatic lesions

The frequencies of lymphatic lesions in various areas of the body are shown in Fig. 3. Lymphatic lesions were most frequent in the pelvis (43.5%), and their numbers decreased as the distance from the pelvis increased.

3.5. Comparison of CT findings between the S-LAM and TSC-LAM groups

Statistically significant differences distinguished the S-LAM from the TSC-LAM groups. Tables 1–3 display those values for pulmonary nodules, air-space consolidation, pneumothorax formation, lymphadenopathy in the pulmonary hilum, renal AML, hepatic AML, and lymphadenopathy in the retrocrural space.

Table 1
Chest CT findings.

Findings	Total (n = 138)	S-LAM (n = 124)	TSC-LAM (n = 14)	P-value
Pulmonary cysts				
Extent (%)				
Total extent	38.9 ± 27.9	38.5 ± 28.4	43.7 ± 23.8	0.51
Small cysts	27.8 ± 20.5	27.0 ± 20.4	36.1 ± 21.0	0.12
Medium cysts	9.2 ± 13.0	9.5 ± 13.5	6.3 ± 7.0	0.38
Large cysts	2.0 ± 4.9	2.1 ± 5.1	1.4 ± 2.3	0.60
Distribution (no. of patients)				
Axial direction				
Upper predominant	8(5.8)	7(5.6)	0	0.48
Lower predominant	12(8.6)	12(9.7)	0	
Random/Diffuse	117(84.2)	104(83.9)	14(100)	
No cyst	1(0.7)	1(0.8)	0	
Horizontal direction				
Central predominant	0	0	0	0.87
Peripheral predominant	0	0	0	
Ventral predominant	3(2.2)	3(2.4)	0	
Dorsal predominant	0	0	0	
Random/diffuse	134(96.4)	120(96.8)	14(100)	
No cyst	1(0.7)	1(0.8)	0	
Pulmonary nodule	52(37.7)	42(33.9)	10(71.4)	<0.01
Nodules of <10	45(32.6)	40(32.3)	5(35.7)	<0.01
Nodules of ≥10	7(5.1)	2(1.6)	5(35.7)	
Size in patients with nodules (mm)	3.8 ± 2.8 (1.0–16.5)	3.4 ± 2.8 (1.0–16.5)	5.3 ± 2.7 (1.5–10)	0.15
Ground-glass attenuation	7(5.1)	7(5.6)	0	0.36
Extent in patients with ground-glass attenuation (%)	14.3 ± 14.2	14.3 ± 14.2	–	N/A
Air-space consolidation	6(4.3)	3(2.4)	3(21.4)	<0.01
Extent in patients with air-space consolidation (%)	4.4 ± 2.5	5.0 ± 2.5	3.9 ± 2.5	0.64
Thickening of bronchovascular bundles	25(18.1)	20(16.1)	5(35.7)	0.07
Interlobular septal thickening	13(9.4)	13(10.5)	0	0.20
Thoracic duct dilatation	5(3.6)	4(3.2)	1(7.1)	0.46
Pneumothorax	14(10.1)	10(8.1)	4(28.6)	0.02
Right side	5(3.6)	3(2.4)	2(14.3)	
Left side	8(5.8)	7(5.6)	1(7.1)	<0.01
Both sides	1(0.7)	0	1(7.1)	
Pleural effusion	15(10.8)	14(11.3)	1(7.1)	0.64
Right side	6(4.3)	5(4.0)	1(7.1)	
Left side	8(5.8)	9(7.3)	0	0.72
Both sides	1(0.7)	0	0	
Thoracic lymphadenopathy	14(10.1)	12(9.7)	2(14.3)	0.59
Mediastinum	10(7.2)	9(7.3)	1(7.1)	0.99
Pulmonary hilum	3(2.2)	1(0.8)	2(14.3)	<0.01
Supraclavicular region	1(0.7)	1(0.8)	0	0.74
Axilla	1(0.7)	1(0.8)	0	0.74

N/A: not available. Data in parenthesis are percentages.

4. Discussion

Our present study is the first to document the results from a large serial study of Japanese patients with LAM. Recently, a group at the American National Institutes of Health (NIH) reported the outcomes for similar analyses of patients with LAM [5,6]. The pathognomonic finding in chest CTs of patients with LAM is thin-walled pulmonary cysts in a random distribution. In our patients, TSC-LAM groups had a higher extent of pulmonary cysts than in some previous reports. The cause of this discrepancy may have been due to the small number of TSC-LAM patients in our study. Nevertheless, in our series, the frequency of pulmonary nodules (18.8% in total, 13.7% in S-LAM, and 64.3% in TSC-LAM) was higher than in the NIH group's study (3.4% in total, 1% in S-LAM, and 12% in TSC-LAM). The racial differences may be one cause of the difference between the two studies, because this disparity in results was confirmed when we used their definition ("multiple [three or more] noncalcified pulmonary nodules") [6].

Ground-glass attenuation and consolidation are thought to represent hemorrhage and/or edema [9]. Moreover, such findings may also indicate lymphatic edema, because six of our patients with these conditions also manifested interlobular septal thickening and/or thickening of the bronchovascular bundles, which could be an expression of interstitial lymphatic edema caused by obstruction of the lymphatic vessels [10,11].

In our series, the frequency of mediastinal lymphadenopathy was 8.7%, with no differences observed between the S-LAM and TSC-LAM groups. However, pulmonary hilar lymphadenopathy was more common in TSC-LAM than in S-LAM group [2,12]. The frequencies of thoracic duct dilatation and pleural effusion found in our patients were similar to those reported in the previous report [6]. Two of our patients exhibited diffusely thickened mediastina with decreased density. The cause may have been an increase of lymphatic fluid accumulated in the mediastinum, because pleural effusions and ground-glass attenuation present in both patients could indicate lymphatic abnormalities.

Renal AML is the most common tumor associated with LAM, and the reported frequency of renal AML is up to 90% among patients with TSC and up to 50% for patients with S-LAM [5,6,13–15]. Our S-LAM patients had a lower frequency of renal AML than in that of previous reports (27.8% in total, 17.4% in S-LAM and 85.7% in TSC-LAM). The racial difference may account for this divergence.

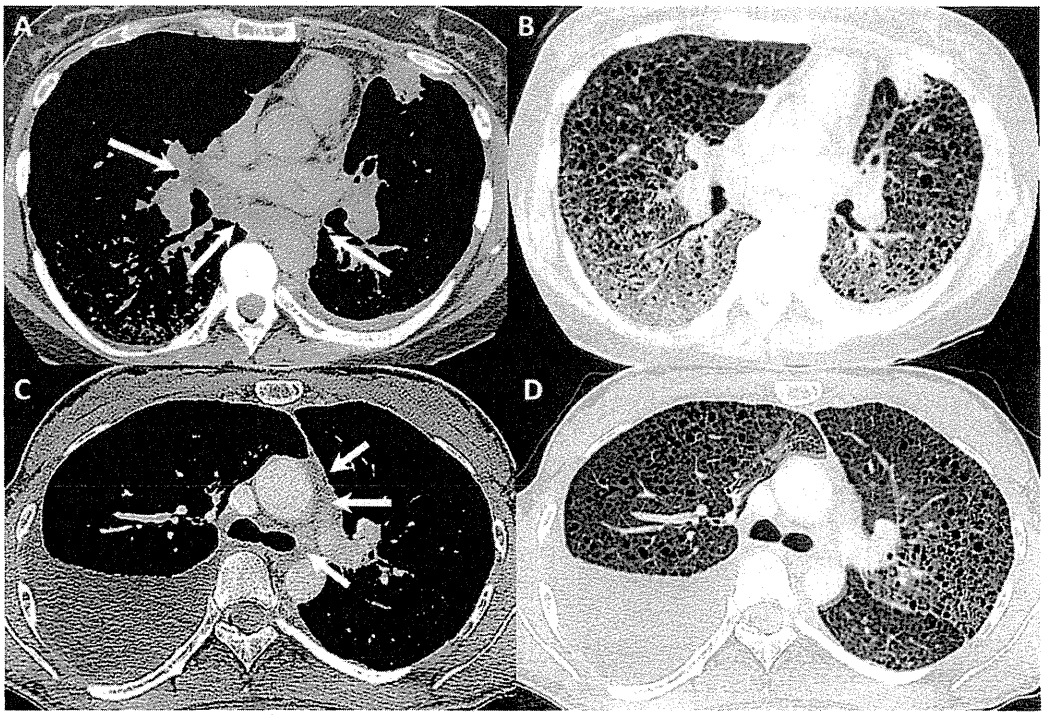

Fig. 2. CT images of a thickened mediastinum with decreased density. (A, B) CT images of a 41-year-old female with S-LAM, and (C, D) CT images of a 30-year-old female with S-LAM. The CT images of both patients show thickened mediastina with decreased density (arrows). Note the coexistence of ground-glass attenuation and pleural effusion.

Hepatic AML is a rare, benign fatty tumor. The NIH group reported the frequency of hepatic AML in LAM patients to be 8.7%, which is lower than our findings (19.4%). In our series, hepatic AML was more common in the TSC-LAM group than in the S-LAM group (57.1% vs. 15.4%, respectively), and this result also differs from that reported by the NIH (33% vs. 2%), possibly owing to racial factors. Others found hepatic AML only in association with renal AML [16]. However, both of our two patients with TSC-LAM as well as hepatic AML also had renal AML. Still, among the S-LAM patients, only four of 15 patients with hepatic AML also had renal AML. Therefore, no association was apparent between the occurrence of hepatic AML and renal AML in patients with S-LAM.

Renal cysts are acquired lesions that are thought to evolve from diverticula in the distal convoluted and collecting tubules [17]. The progression of diverticula into cysts seems to occur primarily as an age-related process in association with weakening of the tubular basement membrane [18]. As documented, the prevalence of renal and liver cysts in Japanese females 35–40 years of age

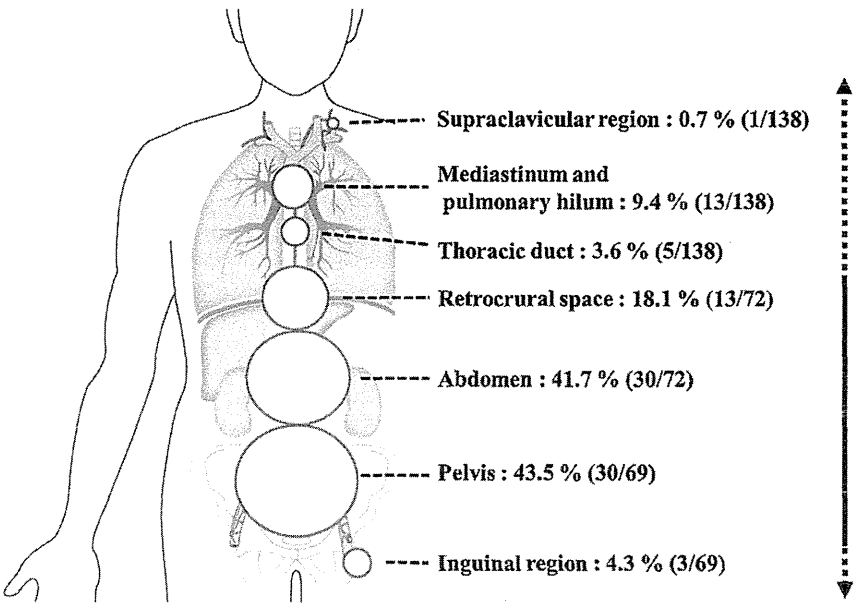

Fig. 3. Frequency of lymphatic lesions. Lymphatic lesions were most frequently observed in the pelvis, with the incidence decreasing as the distance from the pelvis increased.

Table 2
Kidney and liver findings.

Findings	Number of patients			
	Total (n = 72)	S-LAM (n = 65)	TSC-LAM (n = 7)	P-value
Kidney				
AML	20(27.8)	14(21.5)	6(85.7)	<0.01
Fat containing mass	16(24.6)	10(15.4)	6(85.7)	<0.01
Right side	5(6.9)	4(6.2)	1(14.3)	
Left side	3(4.2)	1(1.5)	2(28.6)	<0.01
Both sides	8(12.3)	5(7.7)	3(42.9)	
Fat containing mass of <10	10(15.4)	8(12.3)	3(42.9)	
Fat containing mass of ≥10	5(6.9)	2(3.1)	3(42.9)	<0.01
Size of mass in patients with this finding (mm)	41.8 ± 37.1	51.8 ± 43.8	25.2 ± 11.9	0.17
Uniformly enhanced mass	3(4.2)	2(3.1)	1(14.3)	0.16
Right side	1(1.4)	0	1(14.3)	
Left side	2(2.8)	2(3.1)	0	0.02
Both sides	0	0	0	
Uniformly enhanced mass of <10	3(4.2)	2(3.1)	1(14.3)	
Uniformly enhanced mass of ≥10	0	0	0	0.37
Size of mass in patients with this finding (mm)	15.8 ± 9.5	21.3 ± 1.8	5.0	N/A
Renal artery embolization or renal extraction	5(6.9)	4(6.2)	1(14.3)	0.42
Right side	1(1.4)	0	1(14.3)	
Left side	4(5.6)	4(6.2)	0	0.02
Both sides	0	0	0	
Cyst	4(5.6)	3(4.6)	1(14.3)	0.29
Right side	1(1.4)	0	1(14.3)	
Left side	2(2.8)	2(3.1)	0	0.02
Both sides	1(1.4)	1(1.5)	0	
Cyst of <10	4(5.6)	3(4.6)	1(14.3)	
Cyst of ≥10	0	0	0	0.57
Size of cyst in patients with this finding (mm)	4.1 ± 0.4	4.0 ± 0.5	4.5	N/A
Liver				
AML = Fat containing mass	14(19.4)	10(15.4)	4(57.1)	0.01
Fat containing mass of <10	11(15.3)	9(13.8)	2(28.6)	
Fat containing mass of ≥10	3(4.2)	1(1.5)	2(28.6)	<0.01
Size of mass in patients with this finding (mm)	15.8 ± 19.3	10.6 ± 5.9	28.8 ± 34.5	0.11
Cyst	10(13.9)	10(15.4)	0	0.26
Cyst of <10	10(13.9)	10(15.4)	0	
Cyst of ≥10	0	0	0	0.54
Size of cyst in patients with this finding (mm)	12.8 ± 17.3	12.8 ± 17.3	-	N/A
Hemangioma	1(1.4)	1(1.5)	0	0.74
Hemangioma of <10	1(1.4)	1(1.5)	0	
Hemangioma of ≥10	0	0	0	0.95
Size of hemangioma in patients with this finding (mm)	20.0	20.0	-	N/A

N/A: not available. Data in parenthesis are percentages.

is approximately 1.5% and 2%, respectively [19]. Therefore, our results suggest the probability of a high incidence of renal and hepatic cysts in LAM patients.

Enlarged LNs in the abdomen and pelvis have been described in up to 40% of patients with S-LAM, with 14% occurring in the retrocrural space, 25% in the abdomen, and 5% in the pelvis [11]. Our results showed a relatively lower incidence of lymphadenopathy in these regions. LALM is thought to result from the proliferation of LAM cells in lymphatic vessels, causing dilatation and obstruction [20]. The CT scans of patients with LALM have included large, contiguous, lobulated masses, sometimes infiltrating the retroperitoneum. The NIH group cited a 24.8%, frequency of LALM in LAM patients, which is similar to our results. Solitary masses other than LNs were apparent only in our S-LAM patients. This type of lesion is thought to be a relatively small LALM, since most of these lesions contain areas of low attenuation on CT. However, the LNs in LAM patients can measure up to 4.0 cm in diameter; therefore, some of these lesions may be LNs. Unfortunately, the small number of our TSC-LAM patients precluded a precise statistical analysis of the difference between S-LAM and TSC-LAM.

LAM cells produce VEGF-D that induces lymphangiogenesis where the cells proliferate. Accordingly, patients with LAM frequently show such abnormalities along the axial lymphatics as thoracic duct dilatation, lymphadenopathy, and LALM as well as chyle leakage into the thorax and/or abdomen [21]. The frequencies of findings related to abnormalities of the axial lymphatics in our patients are presented in Fig. 3. Axial lymphatic abnormalities were most common in the pelvis and tended to decrease in incidence with increased distance from the pelvis. This result is consistent with the histopathological incidence of lymphatic lesions identified by Kumasaka et al. in five individuals at autopsy. In their report, the axial lymphatic system, including the retroperitoneal LNs, thoracic duct, mediastinal LNs, and left supraclavicular LNs, exhibited a high rate of positive LAM lesions (88%, 100%, 68%, and 82%, respectively) [21]. However, LNs belonging to the tributaries, such as the mesenteric, axial, and cervical LNs, exhibited no or extremely low rates of positive LAM lesions (0–14%). Taking into consideration the lymphatic stream's direction, we believe the results from both radiologic and histopathologic examinations suggest that LAM cells originate in the pelvic cavity and spread via the axial lymphatic system. This presumption is supported by two pathologic studies: (1) uterine and adnexal involvement by LAM is highly prevalent as demonstrated in 9 of 10 LAM patients examined [22], and (2) LAM lesions in pelvic and paraaortic LNs were found in three patients with uterine cancer, although none of them had TSC or LAM in other organs [23].

Our study has several limitations. First, this is a retrospective, cross-sectional study that lacks longitudinal data and also detailed clinical information (i.e., clinical manifestation and pulmonary function). Second, there is a selection bias because our institution

Table 3
Findings of lymphatic lesions.

	Number of patients			
	Total	S-LAM	TSC-LAM	*P*-value
Lymphadenopathy				
Retrocrural space (n=72)	2(2.8)	1/65(1.5)	1/7(14.3)	0.05
Lymphadenopathy of <10	2(2.8)	1/65(1.5)	1/7(14.3)	0.15
Lymphadenopathy of ≥10	0	0	0	
Abdomen (n=72)	8(11.1)	6/65(9.2)	2/7(28.6)	0.12
Lymphadenopathy of <10	3(4.2)	2/65(3.1)	1/7(14.3)	0.25
Lymphadenopathy of ≥10	5(6.9)	4/65(6.2)	1/7(14.3)	
Pelvis (n=69)	8(11.6)	6/62(9.7)	2/7(28.6)	0.14
Lymphadenopathy of <10	2(2.9)	1/62(1.6)	1/7(14.3)	0.13
Lymphadenopathy of ≥10	6(8.7)	5/62(8.1)	1/7(14.3)	
Inguinal region (n=69)	3(4.3)	3/62(4.8)	0	0.40
Lymphadenopathy of <10	1(1.4)	1/62(1.6)	0	0.84
Lymphadenopathy of ≥10	2(2.9)	2/62(3.2)	0	
Lymphangioleiomyoma				
Retrocrural space (n=72)	10(13.9)	8/65(12.3)	2/7(28.6)	0.24
Abdomen (n=72)	23(31.9)	21/65(32.3)	2/7(28.6)	0.84
Pelvis (n=69)	17(24.6)	15/62(23.1)	2/7(28.6)	0.75
Extent of lymphangioleiomyoma (n=69)				
Only in the retrocrural space	1(1.4)	1/62(1.6)	0	0.27
Only in the abdomen	5(6.9)	5/62(8.1)	0	
Only in the pelvis	2(2.9)	1/62(1.6)	1/7(14.3)	
From retrocrural space to abdomen	3(4.2)	2/62(3.2)	1/7(14.3)	
From abdomen to pelvis	9(13.0)	9/62(14.5)	0	
From retrocrural space to pelvis	6(8.7)	5/62(8.1)	1/7(14.3)	
Solitary masses				
Retrocrural space (n=72)	2(2.8)	2/65(3.1)	0	0.64
Solitary mass of <10	2(2.8)	2/65(3.1)	0	0.90
Solitary mass of ≥10	0	0	0	
Size of mass in patients with this finding (mm)	22.0±12.0	22.0±12.0	–	N/A
Abdomen (n=72)	1(1.4)	1/65(1.5)	0	0.74
Solitary mass of <10	1(1.4)	1/65(1.5)	0	0.95
Solitary mass of ≥10	0	0	0	
Size of mass in patients with this finding (mm)	11.5	11.5	–	N/A
Pelvis (n=69)	9(13.0)	7/62(11.3)	2/7(28.6)	0.20
Solitary mass of <10	7(10.1)	6/62(9.7)	1/7(14.3)	0.15
Solitary mass of ≥10	2(2.9)	1/62(1.6)	1/7(14.3)	
Size of mass in patients with this finding (mm)	29.6±7.4	27.7±7.4	36.3±1.8	0.17
Inguinal region (n=69)	0	0	0	N/A

N/A: not available. Data in parenthesis are percentages.

is a referral center, and the number of TSC-LAM patients included was relatively small. Moreover, because our study was a retrospective study about the patients with LAM who were referred to the respiratory department of our institution, relatively lower percentage of patients underwent abdominal and pelvic CT. However, to our knowledge, the number of patients included to our study ranks second to that in the report of Avila et al. [6]. Our result is not based on many patients with severe disease or comorbidities, because all patients were studied when there was no evidence of large pneumothorax and infection. Third, regarding evaluation of the size of intrapelvic solitary masses, the correlation between the two reader groups was not statistically significant (r=0.215, P=0.580), because so few patients had this condition. Fourth, this study is a multicenter investigation and the CT scans were obtained with a variety of scanners. However, there was little difference in CT image quality because the scanning protocols were almost uniform. Finally, not all findings exhibited pathologic correlations.

In conclusion, this study is the first to delineate in detail CT findings in a large series of Japanese patients with LAM. Notably, the incidence of some CT findings in our study differs from those in previous reports, possibly attributable to racial variations. An examination of lymphatic lesions suggests that LAM cells may originate in the pelvis then spread via the axial lymphatic system. Because medical diagnosis and treatment are subject to the uniqueness of human populations, global comparisons significantly enhance our ability to alleviate disease.

Conflict of interest

The authors declare there are no conflicts of interest.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejrad.2014.12.008.

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Letter to the Editor

What's the role of sirolimus on the treatment of lymphangioleiomyomatosis (LAM)?: Merely tuning up of LAM-associated dysfunctional lymphatic vessels rather than cytoreduction?

To the Editor,

In a recent study, we reported the efficacy and safety of low sirolimus doses for the treatment of lymphangioleiomyomatosis (LAM) [1]. One of the representative LAM patients, JUL97 had complicated Aspergillus infection in a large destructive airspace caused by LAM in her right upper lobe while she was being administered sirolimus and had undergone right upper lobectomy. The sirolimus trough level in the blood was 1.2 ng/mL. Montero et al. had previously reported the radical reduction in the number of LAM cells in explanted lungs from six patients treated with sirolimus before lung transplantation [2]. On the contrary, the pathologic findings of our patient supported the notion that sirolimus exerts cytostatic rather than cytoreductive effects on LAM cells (Fig. 1).

LAM is associated with the dysregulated mammalian target of rapamycin complex 1 (mTORC1) signaling, a key regulatory pathway of protein synthesis, cell growth, and energy metabolism due to TSC gene mutation. This pathobiologic mechanism is the basis for molecular targeting of mTORC1 by sirolimus in LAM patients. The Multicenter International Lymphangioleiomyomatosis Efficacy and Safety of Sirolimus (MILES) trial successfully demonstrated that sirolimus stabilized pulmonary function in LAM patients; however, cessation of sirolimus therapy caused recurrence of progressive pulmonary function decline [3]. This supports the hypothesis that sirolimus is cytostatic.

Undoubtedly, sirolimus brought a great clinical impact on our patient since (1) she got rid of pulmonary lymphedema, a copious amount of chylohemosputum, and supplemental oxygen, (2) pulmonary function greatly improved, so that the right upper lobectomy was enabled to perform, and (3) she has been inactive for lung transplantation even after right upper lobectomy as far as she continues to take sirolimus [1]. We tried to determine the reason for the significant clinical impact observed in spite of the remaining large LAM cell number. Sirolimus is reported to be a potent inhibitor of lymphangiogenesis even at doses as low as 1 ng/mL [4] as well as to down-regulate the expression of vascular endothelial growth factor receptor-3 (VEGFR-3) by lymphatic endothelial cells [5]. In addition, sirolimus also decreased the serum levels of VEGF-D, a potent lymphangiogenic growth factor produced by LAM cells [3]. Our patient did have a lowered serum VEGF-D level while on sirolimus [1]. Resolution of pulmonary lymphedema as well as chylous pleural effusion and/or ascites with sirolimus therapy has also been reported by others [6]. Based on these findings, we hypothesize that the patient in this case benefited greatly from the low sirolimus doses owing to the fact that sirolimus inhibits LAM-associated lymphangiogenesis and "tunes up" their dysfunctional and leaky properties instead of reducing the number of LAM cells.

Conflict of interest

Kuniaki Seyama was paid travel expenses by the LAM foundation to attend the LAMposium 2013 in Cincinnati. The other authors have no conflicts of interest.

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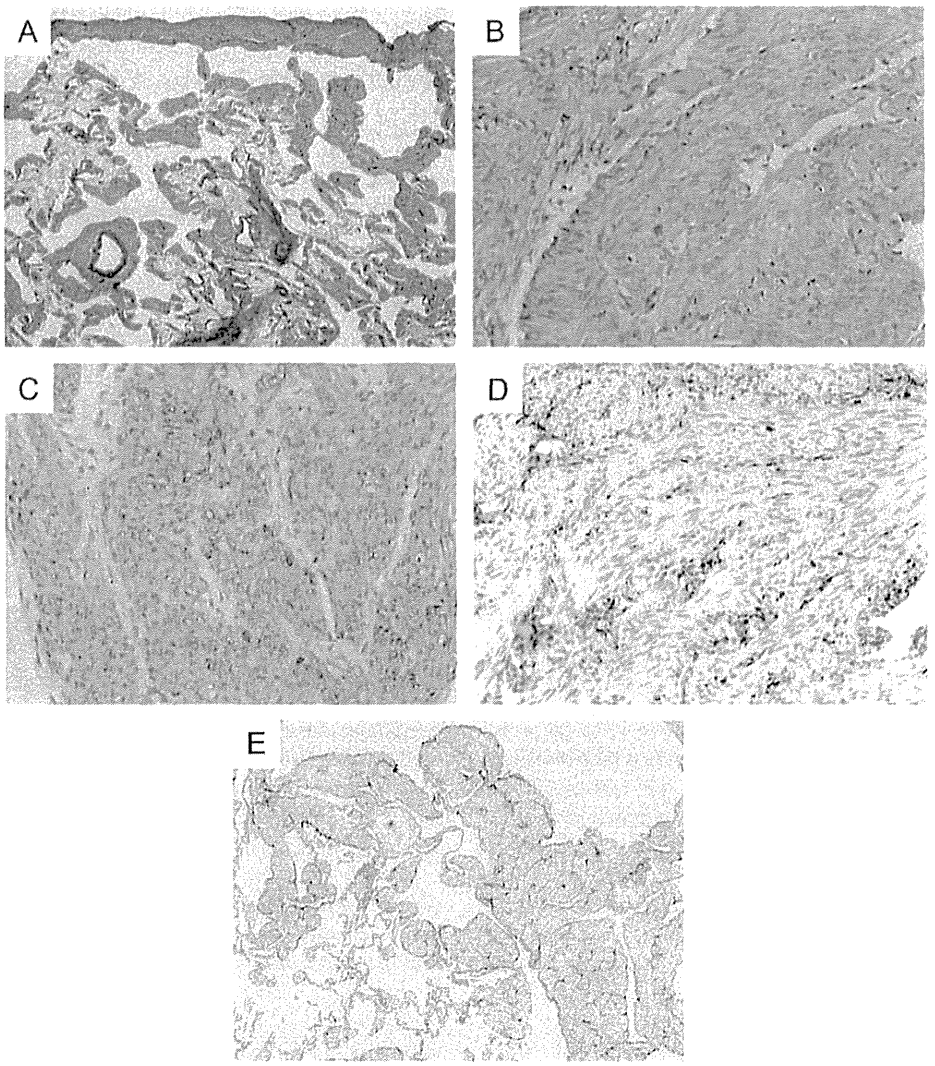

Fig. 1 – Histopathlogical findings of the resected right upper lobe post sirolimus treatment. The excised lung contained a large number of LAM cells in the parenchyma and visceral pleura ((A) Masson–Trichrome stain). A minimal amount of collagen tissue was noted within the LAM nodules. A high-magnification photomicrograph demonstrated bundles of spindle-shaped cells with cigar-shaped nuclei and eosinophilic cytoplasm proliferated in a nodular and whirling pattern ((B) hematoxylin–eosin stain). The proliferating cells were immunopositive for α-smooth muscle actin (C) as well as for HMB45 (D); therefore, they were confirmed to be LAM cells. However, slit-like clefts within the LAM nodule, indicative of LAM-associated lymphatic vessels, were not as noticeable as usual. This was confirmed by imunohistochemical analysis with a lymphatic endothelial cell ((E) D2-40 immunostaining) marker.

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Kentaro Suina M.D.*, Kazuhisa Takahashi
Division of Respiratory Medicine, Juntendo University Faculty of Medicine and Graduate School of Medicine, 2-1-1 Hongo, Bunkyo-Ku, Tokyo 113-8421, Japan
E-mail addresses: ksuina@juntendo.ac.jp (K. Suina), katakaha@juntendo.ac.jp (K. Takahashi)

Takuo Hayashi, Keiko Mitani
Department of Human Pathology, Juntendo University Faculty of Medicine and Graduate School of Medicine, 2-1-1 Hongo, Bunkyo-Ku, Tokyo 113-8421, Japan
E-mail addresses: tkhyz@juntendo.ac.jp (T. Hayashi), m-kei@juntendo.ac.jp (K. Mitani)

Kenji Suzuki
Department of Thoracic Surgery, Juntendo University Faculty of Medicine and Graduate School of Medicine, 2-1-1 Hongo, Bunkyo-Ku, Tokyo 113-8421, Japan
E-mail address: kjsuzuki@juntendo.ac.jp

Kuniaki Seyama
Division of Respiratory Medicine, Juntendo University Faculty of Medicine and Graduate School of Medicine, 2-1-1 Hongo, Bunkyo-Ku, Tokyo 113-8421, Japan
The Study Group of Pneumothorax and Cystic Lung Diseases, 4-8-1 Seta, Setagaya-Ku, Tokyo 158-0095, Japan
E-mail address: kseyama@juntendo.ac.jp

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*Corresponding author. Tel.: þ 81 3 5802 1063; fax: þ 81 3 5802 1617.

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Thoracic Endometriosis-Related Pneumothorax Distinguished From Primary Spontaneous Pneumothorax in Females

Takahiro Haga · Hideyuki Kataoka · Hiroki Ebana · Mizuto Otsuji · Kuniaki Seyama · Koichiro Tatsumi · Masatoshi Kurihara

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Abstract
Purpose Thoracic endometriosis-related pneumothorax (TERP) is a secondary condition specific for females, but in a clinical setting, TERP often is difficult to distinguish from primary spontaneous pneumothorax (PSP) based on a relationship between the dates of pneumothorax and menstruation. The purpose of this study was to clarify the clinical features of TERP compared with PSP.
Methods We retrospectively reviewed the clinical and histopathological files of female patients with pneumothorax who underwent video-assisted thoracoscopic surgery in the Pneumothorax Research Center during the 6-year period from January 2005 to December 2010. We analyzed the clinical differences between TERP and PSP.
Results The study included a total of 393 female patients with spontaneous pneumothorax, of whom 92 (23.4 %) were diagnosed as having TERP and 33.6 % (132/393) as having PSP. We identified four factors (right-sided pneumothorax, history of pelvic endometriosis, age ≥31 years, and no smoking history) that were statistically significant for predicting TERP and assigned 6, 5, 4, and 3 points, respectively, to establish a scoring system with a calculated score from 0 to 18. The cutoff values of a calculated score ≥12 yielded the highest positive predictive value (86 %; 95 % confidence interval (CI) 81.5–90.5 %) for TERP and negative predictive value (95.2 %; 95 % CI 92.3–98 %) for PSP.
Conclusions TERP has several distinct clinical features from PSP. Our scoring system consists of only four clinical variables that are easily obtainable and enables us to suspect TERP in female patients with pneumothorax.

Keywords Primary spontaneous pneumothorax · Thoracic endometriosis-related pneumothorax · Thoracic endometriosis · Pneumothorax

A1 T. Haga · H. Kataoka · H. Ebana · M. Otsuji · M. Kurihara (✉)
A2 Pneumothorax Research Center and Division of Thoracic
A3 Surgery, Nissan Tamagawa Hospital, 4-8-1 Seta,
A4 Setagaya-ku, Tokyo 158-0095, Japan
A5 e-mail: kuri@tf6.so-net.ne.jp

A6 T. Haga · K. Tatsumi
A7 Department of Respirology, Graduate School of Medicine, Chiba
A8 University, 1-8-1 Inohana, Chuo-ku, Chiba 260-8670, Japan

A9 T. Haga · H. Kataoka · H. Ebana · M. Otsuji · K. Seyama ·
A10 M. Kurihara
A11 The Study Group of Pneumothorax and Cystic Lung Diseases,
A12 4-8-1 Seta, Setagaya-ku, Tokyo 158-0095, Japan

A13 H. Ebana · K. Seyama
A14 Division of Respiratory Medicine, Juntendo University Faculty
A15 of Medicine and Graduate School of Medicine, 2-1-1 Hongo,
A16 Bunkyo-ku, Tokyo 113-8421, Japan

A17 H. Ebana · M. Otsuji
A18 Division of Thoracic and Cardiovascular Surgery, Tokyo
A19 Metropolitan Bokutoh Hospital, 4-23-15 Koto-bashi,
A20 Sumida-ku, Tokyo 130-8575, Japan

Introduction

Spontaneous pneumothorax is classified into primary (PSP) and secondary categories. PSP refers to a spontaneously occurring air leakage into the pleural space in patients with no clinically apparent underlying lung disease [1]. The diagnosis of PSP is confirmed histopathologically with subpleural blebs and bullae and no obvious abnormality in pulmonary parenchyma [2]. Catamenial pneumothorax is a condition limited to females and reported to account for approximately 20–30 % of women with pneumothorax [3, 4]. It is defined simply by the onset of pneumothorax

during a menstrual cycle: the pneumothorax that occurs between 24 h before and 72 h after the initiation of menses [5]. Because catamenial pneumothorax is usually caused by thoracic endometriosis [6, 7], a large part of catamenial pneumothorax is diagnosed as thoracic endometriosis-related pneumothorax (TERP) after thoracic surgery. However, catamenial pneumothorax may include female patients with PSP that happens to occur in the perimenstrual period.

TERP is defined as pneumothorax due to thoracic endometriosis, and the diagnosis of TERP requires histopathological confirmation [5]. Generally, ectopic endometrial tissues are found in the diaphragm in TERP, whereas no abnormality in pulmonary parenchyma is apparent. The mechanism of TERP has been speculated as follows: (1) air enters into the thoracic cavity from the peritoneum through a diaphragmatic defect caused by the implantation of endometrial tissues. This air in the peritoneum may be from outside the body and pass through ovarian tubes [8]. (2) Alternatively, air enters into the thoracic cavity from the airway through a defect of visceral pleura caused by the implantation of endometrial tissues [9, 10].

Until recently, TERP had been thought to develop only as catamenial pneumothorax. However, Alifano et al. [11] recently reported that 37.9 % of TERP cases developed as non-catamenial pneumothorax. Accordingly, TERP is difficult to distinguish from PSP based on the relationship between the calendar dates of pneumothorax and menstruation; theoretically, catamenial TERP, non-catamenial TERP, catamenial PSP, and non-catamenial PSP exist. Furthermore, TERP is virtually indistinguishable from PSP based on the findings of imaging tests, such as chest X-ray and computed tomography (CT), because the amount of ectopic endometrial tissue implanted within the respiratory system is too small for detection by such examinations [5]. A preferable scenario is that TERP is suspected before surgery, because the approaches for therapy as well as the recurrence rate [12, 13] are quite different between TERP and PSP.

As previously described, the clinical features of TERP are right-sided pneumothorax and a history of pelvic endometriosis [5]. In contrast, patients with PSP tend to be tall [14] and usually have a smoking history [15, 16]. However, few reports have compared directly the clinical features of TERP and PSP nor do they clarify the significance of each clinical variable. The purpose of this study was to clarify the clinical features of TERP compared with PSP.

Methods

Study Population

The clinical and histopathological files of all female patients who underwent video-assisted thoracoscopic surgery (VATS) in the Pneumothorax Research Center during the 6-year period from January 2005 to December 2010 were retrospectively reviewed. The patients who were histopathologically diagnosed as having TERP or PSP were included in this study. According to Alifano et al. [11], we made a diagnosis of TERP when the existence of endometrial stroma or the endometrial glands in the resected diaphragm and/or lung tissue was confirmed immunohistochemically by the presence of strong nuclear staining for either estrogen or progesterone receptors. The diagnosis of PSP was made when (1) pneumothorax occurred in otherwise healthy individuals with normal or essentially normal underlying lungs on CT images of the chest, and (2) blebs and/or bullae were histologically confirmed in the resected lung specimen. In patients with PSP, we were unable to collect information from medical records on the relationship between the occurrence of pneumothorax and menstrual cycle.

For patients with TERP and PSP, we compared the ages, pneumothorax side, height, body weight, smoking habits, history of pelvic endometriosis, number of pneumothorax episodes before surgery, duration of follow-up after surgery, and postoperative recurrence rate. We assigned the scores to each clinical variables found to be an independent predictor for the diagnosis of TERP, weighted according to the beta-coefficients from the multivariate logistic model [17]. We calculated a total score for each patient and analyzed the performance characteristics of the score for the diagnosis of TERP. The study was approved by the institutional review board of Nissan Tamagawa Hospital (approval number 12-012).

Statistical Analysis

The quantitative data are presented as mean ± SD. The differences between the patients with TERP and PSP were analyzed using the Chi square test for categorical variables and Student's t test for quantitative variables. A multiple logistic regression analysis was used to assess the role of several variables as predictive factors for TERP. The contribution of each potential predictive factor was denoted by an odds ratio and the associated 95 % confidence interval (CI). A receiver operating characteristic (ROC) curve was used to analyze the probability of TERP diagnosis in dependence on the calculated score. A value of $p < 0.05$ was considered to be significant. A statistical software package (JMP, version 10.0.2; SAS Institute; Cary, NC) was used for the statistical analysis.

Results

In total, 562 female patients with spontaneous pneumothorax were admitted for treatment during the 6-year study

Table 1 Characteristics of study population

	Patients with TERP ($n = 92$)	Patients with PSP ($n = 132$)	p value
Age (years) (range)	38.6 ± 5.7 (24–50)	27.7 ± 9.8 (14–67)	<0.01
Side of pneumothorax			
Right	91 (98.9 %)	56 (42.4 %)	<0.01
Left	1 (1.1 %)	76 (57.6 %)	
Height (cm)	159.0 ± 4.9	160.9 ± 5.9	<0.05
Weight (kg)	49.1 ± 5.7	47.6 ± 6.1	0.074
Smoking habit			
Current/former smoker	6 (6.5 %)	41 (31.1 %)	<0.01
Nonsmoker	86 (93.5 %)	91 (68.9 %)	
History of pelvic endometriosis	54 (58.7 %)	3 (2.3 %)	<0.01
The number of preoperative pneumothorax episodes	8.1 ± 3.2	2.8 ± 1.6	<0.01
Postoperative follow-up period (months)	36.2 ± 22.3	12.0 ± 11.8	<0.01
Number of patient with postoperative recurrence	36 (39.1 %)	23 (17.4 %)	<0.01

period. Of these, 393 patients underwent VATS for pneumothorax. Ninety-two (23.4 %) of the 393 patients were diagnosed as having TERP and 33.6 % (132/393) as having PSP. Thirty (32.6 %) of the 92 patients with TERP had catamenial pneumothorax with the remainder (62/92, 67.4 %) classified as non-catamenial.

Characteristics of the study population are summarized in Table 1. The patients with TERP showed significantly distinct features differing from those in the patients with PSP. The TERP group was older, shorter, and usually had right-sided pneumothorax plus pelvic endometriosis but little or no history of smoking. Many preoperative pneumothorax episodes were noted. One exception was a patient with TERP whose pneumothorax was left-sided. The postoperative recurrence of pneumothorax was more frequently noted in patients with TERP.

To find the predictive factors for TERP, we performed multivariable analysis (Table 2). The right-sided pneumothorax showed the greatest odds ratio among the other predictive factors, followed by history of pelvic endometriosis, age ≥31 years, no smoking history, the number of preoperative pneumothorax episodes ≥4, and height ≤159 cm in that order.

Next, we assigned a score to each predictive factor to establish discriminant analysis between TERP and PSP. We excluded two factors—height and the number of preoperative pneumothorax episodes—from the discriminant analysis, because these are likely to be greatly influenced

Table 2 Factors predicting TERP

Risk factors	Odds ratio	95 % CI	p value	Score assigned[a]
Right pneumothorax	440.3	15–12943.4	<0.01	6
History of pelvic endometriosis	115.1	10.2–1306.2	<0.01	5
Age ≥31 year	78.0	12.1–502.1	<0.01	4
No history of smoking	13.4	3–61	<0.01	3
Number of preoperative pneumothorax episodes ≥4	5.8	1.4–23.6	<0.05	NA
Height ≤159 cm	4.1	1.2–14.2	<0.05	NA

Calculated score = Right pneumothorax (score 6 or 0) + history of pelvic endometriosis (score 5 or 0) + age ≥31 years old (score 4 or 0) + no history of smoking (score 3 or 0)

NA not adopted

[a] If each risk factor does not exist, the score "0" is given in the following equation

by race and the medical treatment available for pneumothorax; additionally, these two factors interfered with generalizing the outcome. Accordingly, we adopted the four factors to which scores of 3–6 were assigned then established a system with calculated scores from 0 to 18 (Table 2). These scores were tested at different cutoff values. The cutoff values of a calculated score ≥12 yielded the highest positive predictive value (86 % with 95 % CI 81.5–90.5 %) for TERP and negative predictive value (95.2 % with 95 % CI of 92.3–98 %) for PSP (Table 3). The ROC curve reflects the accuracy of the diagnostic test: area under the curve was 0.9665 (Fig. 1).

Discussion

We found that TERP had distinct clinical features compared with those of PSP, enabling us to establish a simple scoring system to distinguish TERP from PSP. We demonstrated that this system had a satisfactorily high positive predictive value for TERP as well as a negative one for PSP. The scoring system utilizes four clinical variables identified here that are easily obtainable by history taking and physical examination: the side of pneumothorax, history of pelvic endometriosis, patient age, and smoking history. These clinical variables have been reported in the literature to be associated with TERP or PSP [5, 14–16]. Although a concrete diagnosis of TERP is required for histologic examination of the diaphragm or the lung tissue, the scoring system developed here seems to be suitable for suspecting TERP, thereby reducing the oversight of TERP in female patients with pneumothorax.

Table 3 Diagnostic significance of calculated score to differentiate between TERP and PSP

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Calculated score ≥12	0.935 (0.902–0.967)	0.894 (0.854–0.934)	0.86 (0.815–0.905)	0.952 (0.923–0.98)

Numbers in parentheses indicate 95 % confidence interval

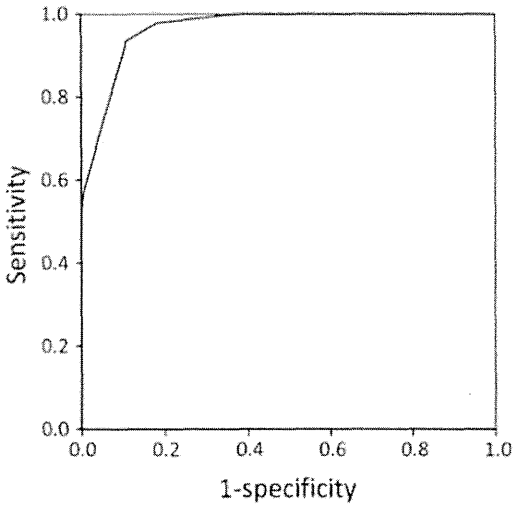

Fig. 1 ROC curve for the prediction of TERP using the calculated score. Note that the score of 12 gives 93.5 % of sensitivity and 89.4 % of specificity. The method for calculating the score appears in the footnote of Table 2

Catamenial pneumothorax has been reported to occur on the right side in almost all such cases [5], and only two case reports of left catamenial pneumothorax [9, 18] and two case reports of bilateral catamenial pneumothorax [19, 20] exist. However, those reports lacked information about the histopathological diagnosis of thoracic endometriosis. This study thus provides the first description of a left-sided TERP based on a histopathological diagnosis. PSP has no documented laterality so far [2]. Therefore, the presence of left pneumothorax in females has a high diagnostic value for PSP.

Evaluating the past history of pelvic endometriosis is valuable for diagnosing TERP in female patients with pneumothorax. In this study, 58.7 % (54/92) of the patients with TERP had a history of pelvic endometriosis. The percentage of patients with pelvic endometriosis among those with catamenial pneumothorax varies broadly and is reported to be 18–84 % [4, 21]. In the majority of patients with thoracic endometriosis, the condition is believed to have spread from pelvic endometriosis [5]. Therefore, the variations in published results are likely due to the different methods used to diagnose pelvic endometriosis. A definitive diagnosis of pelvic endometriosis requires diagnostic laparoscopy, and results from that procedure indicate that the prevalence of pelvic endometriosis among patients of reproductive age is 5–10 % [22]. In the present study, 2.3 % (3/132) of the patients with PSP had a history of pelvic endometriosis.

Previous analyses of catamenial pneumothorax calculated a mean age within the 30 s with a range in such patients from 15 to 54 years [5]. However, patients with PSP are often in their early 20 s but rarely beyond the age of 40 years [2]. The mean age of patients with TERP examined in this study was approximately 10 years older than that of patients with PSP. Therefore, it is important to consider the patient's age when diagnosing TERP in female patients with pneumothorax.

Habitual smoking has been associated with a risk of developing PSP [15, 16]; additionally, patients with PSP tended to be taller than control patients in a previous study [14]. Elsewhere, TERP did not correlate with either the patients' height or habitual smoking [5]. The results of our study are consistent with these findings.

This study has several limitations. First, our subjects were located at the Pneumothorax Research Center, which is specialized for the treatment of pneumothorax and where many patients with intractable pneumothorax are referred. Accordingly, clinical features for TERP and PSP may be biased. Second, we included only the patients with PSP whose diagnoses were confirmed histologically. Because we usually resect lung tissue only when large and/or multiple bullae are apparent during surgery, the patients with PSP in our study may represent a biased population that is not representative for PSP. Third, we could not have evaluated the significance of the onset of pneumothorax during a menstrual cycle as a factor in differentiating TERP from PSP, because no information about the relationship of pneumothorax onset and menstrual period was obtainable for the patient with PSP. Finally, because this was a retrospective cohort study, a prospective study to validate our scoring system is needed.

In conclusion, we have established a scoring system for the diagnosis of TERP that is based on the assignment of weighted values to easily include four clinical variables. This system has a highly positive predictive value for TERP as well as a negative predictive value for PSP. This logical scheme provides a useful tool for predicting TERP in the care of female patients with pneumothorax.

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Conflict of interest None of the authors has any conflicts of interest with regard to this study.

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INTERNAL MEDICINE

□ CASE REPORT □

Cystic, Nodular and Cavitary Metastases to the Lungs in a Patient with Endometrial Stromal Sarcoma of the Uterus

Akiko Murakami[1], Takuo Hayashi[2,3], Yasuhisa Terao[4], Takanori Mori[1], Toshio Kumasaka[3,5], Kuniaki Seyama[1,3] and Kazuhisa Takahashi[1]

Abstract

A 57-year-old woman, who had undergone hysterectomy for uterine myoma 11 years earlier presented with cystic, nodular and cavitary lesions simultaneously visible on computed tomography images of the chest. Histological examinations of both the resected lung and past "myoma" specimens demonstrated that the original uterine tumor was a low-grade endometrial stromal sarcoma (ESS) that had metastasized to the lungs. No previous reports have described the coexistence of cystic, nodular and cavitary lesions with pulmonary metastasis of ESS; however, we successfully correlated the radiologic appearance with the corresponding pathologic findings. Medroxyprogesterone acetate therapy has effectively kept the patient asymptomatic for approximately five years.

Key words: pulmonary metastases, endometrial stromal sarcoma, pneumothorax, progesterone

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Introduction

Low-grade endometrial stromal sarcoma (ESS), a rare neoplasm comprising 0.2% of all uterine cancers and 15% of all uterine sarcomas (1), is classified separately from undifferentiated endometrial sarcoma. Low-grade ESS is histologically similar to proliferating endometrial stromal tissue, exhibits little cytological atypia or pleomorphism and is low in mitotic activity. The prognosis of patients with low-grade ESS is favorable in general, with a 10-year disease-free survival rates of 93% (2). However, approximately 40% of patients with low-grade ESS develop recurrent disease after long tumor-free intervals due to the slow-growing nature of the tumor (3). The major location of distant metastases is the lungs, with an incidence of pulmonary metastasis of 7% to 28% (4).

Pulmonary metastasis of low-grade ESS can manifest as various patterns on computed tomography (CT) images of the chest, including the presence of a solitary nodule, multiple nodules, multiple cysts and reticulonodular infiltrates (4-8). In patients with nodular pulmonary metastases of low-grade ESS, the differential diagnosis includes benign metastasizing leiomyoma (BML), carcinoid tumors, sclerosing hemangioma and metastasis of other neoplasms. On the other hand, cystic metastasis of low-grade ESS in the lungs should be carefully discriminated from lymphangioleiomyomatosis (LAM), mesenchymal cystic hamartoma and metastasis of leiomyosarcoma. However, the simultaneous coexistence of all of these imaging features in a single patient would result in a diagnostic dilemma.

In just such an experience, we encountered a patient with pulmonary metastasis of low-grade ESS who presented with cystic, nodular and cavitary lesions simultaneously. The patient had undergone hysterectomy and bilateral salpingo-oophorectomy due to uterine leiomyoma 11 years earlier. Pathologic and immunohistochemical examinations of her lung specimens greatly contributed to the ability to obtain a proper diagnosis, a rare pattern of pulmonary metastases of low-grade ESS, and provided a plausible explanation for the

[1]Division of Respiratory Medicine, Juntendo University Faculty of Medicine and Graduate School of Medicine, Japan, [2]Division of Human Pathology, Juntendo University Faculty of Medicine and Graduate School of Medicine, Japan, [3]The Study Group of Pneumothorax and Cystic Lung Diseases, Japan, [4]Division of Gynecology and Obstetrics, Juntendo University Faculty of Medicine and Graduate School of Medicine, Japan and [5]Department of Pathology, Japanese Red Cross Medical Center, Japan
Received for publication October 24, 2013; Accepted for publication November 28, 2013
Correspondence to Dr. Akiko Murakami, amuraka@juntendo.ac.jp